Pharmacokinetics and Pharmacology of Anti-Tuberculosis Drugs

Bhavna Narsai, Rph
King County Public Health
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Content to cover

- Intro and History of the drugs
- First-Line Treatments
- Second-Line Treatments
- Third-Line/Other Treatments
- Management of Adverse Reactions
- NEWS?
**Introduction**

- Robert Koch discovered *Mycobacterium tuberculosis* in 1885
- In 2016 worldwide 10.6 million people became sick with TB and 1.7 million TB-related deaths.
- Over 10 million people in the US are infected and they have a lifelong risk of developing TB
- Without treatment, approximately 5-10% of patients with latent TB will progress to active TB disease at some point in their lifetime
- Isoniazid (INH) can reduce the incidence of active TB about 90%
- Before drugs, the treatment was rest in the open air, in specialized sanatorium

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**Tuberculosis Drug Discovery/ Development and Its Impact on Treatment**

- 1944 – Para-aminosalicylic acid (PAS)
- 1946 – Streptomycin (SM)
- 1946 – Thioacetazone
- 1952 – Isoniazid (INH)
  - Replaces sanatorium as major treatment
  - Patients can be treated as out-patient
- 1954 – Pyrazinamide (PZA)
  - Combination therapy of INH and PZA cures TB
- 1955 - Cycloserine (CS)
- 1957 - Kanamycin/amikacin (AK)
- 1965 – Rifampin (RIF)
  - Combination of rifampin and INH adopted as international regimen for treatment of TB
- 1966 – Ethionamide (ETA)
- 1967 – Capreomycin (CM)
- 1968 – Ethambutol (EMB)
The Evolution of Treatment for Active TB

1952 -------------> 1986

250 regimens tested in 25,000 patients in order to determine optimal:
• Drug combinations
• Doses
• Dosing intervals
• Treatment duration

Isoniazid (INH)
• 9-month INH daily
• 9-month INH twice weekly (under DOT)
• 6-months regimen generally acceptable
• Children, HIV-infected, persons whose x-rays suggest previous TB should always receive 9-month treatment

3HP
• INH and Rifapentine once weekly for 12 weeks (under DOT)
• Preferred regimen for children 5 and older
• Should not be used in children younger than 2 due to lack of pharmacokinetic data or established dosing
LTBI Treatment-continued

- **Rifampin (RIF)**
  - 4-month daily (if unable to tolerate INH)
  - If RIF cannot be used, rifabutin can be substituted

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TB Disease Treatment Regimens

- **Initial Phase (2-month):**
  - Isoniazid + Rifampin + Pyrazinamide + Ethambutol
    - EMB may be discontinued as soon as the results of drug susceptibility testing confirm INH and RIF susceptibility

- **Continuation Phase**
  - 1) 7 days/week x 18 weeks and 5 days/week x 18 weeks (for newly diagnosed pulmonary TB).
  - 2) 3 times per week x 18 weeks (where DOT during continuation phase is difficult to achieve). Range of doses 110-94.
  - 3) 3 times per week x 18 weeks (used with caution in patients with HIV or cavitary pulmonary disease). Dose range 78
  - 4) Twice weekly x 18 weeks (do not use in HIV infected patients or those with smear positive and or cavitary disease)
Intermittent Treatment

- Initial 4-drug regimens with 2-3 doses per week are effective (only given by DOT)
- Once-weekly continuation phase:
  - Used for HIV-negative patients
  - Non-cavitary drug-susceptible TB
  - Not for children, pregnant women, extrapulmonary TB

Treatment of TB Disease

<table>
<thead>
<tr>
<th>First-Line Drugs (old)</th>
<th>First-Line Drugs (new 2016)*:</th>
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<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>Isoniazid (INH)</td>
</tr>
<tr>
<td>Rifampin (RIF)</td>
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<tr>
<td>Ethambutol (EMB)</td>
<td>Rifabutin (RFB)</td>
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<td>Pyrazinamide (PZA)</td>
<td>Rifapentine (RPT)</td>
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<tr>
<td>Streptomycin (SM)</td>
<td>Ethambutol (EMB)</td>
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<td>Pyrazinamide (PZA)</td>
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## Treatment of TB Disease

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<tbody>
<tr>
<td>Ethionamide (ETA)</td>
<td>Levofloxacin, moxifloxacin</td>
</tr>
<tr>
<td>Para-aminosalicylic acid (PAS)</td>
<td>Streptomycin (SM), amikacin (AK), kanamycin (KM)</td>
</tr>
<tr>
<td>Cycloserine (CS)</td>
<td>Capreomycin (CM)</td>
</tr>
<tr>
<td>Capreomycin (CM)</td>
<td>Cycloserine (CS)</td>
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<tr>
<td>Kanamycin (KM)</td>
<td>Para-aminosalicylic acid (PAS)</td>
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<td>Ethionamide (ETA)</td>
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## First Versus Second Line:

- Efficacy
- Toxicity
- Tolerability
- Experience
### Efficacy

<table>
<thead>
<tr>
<th>Bactericidal:</th>
<th>Bacteriostatic:</th>
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</thead>
<tbody>
<tr>
<td><em>ability to kill</em></td>
<td><em>ability to inhibit the multiplication of the organism</em></td>
</tr>
<tr>
<td>Isoniazid (INH)</td>
<td>Ethambutol (EMB) in low doses</td>
</tr>
<tr>
<td>Rifamycins (rifampin, rifabutin)</td>
<td>Para-salicyclic acid (PAS)</td>
</tr>
<tr>
<td>Pyrazinamide (PZA)</td>
<td>Ethionamide (ETA) – weakly bactericidal</td>
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<tr>
<td>Aminoglycosides (STM, AK, KM)</td>
<td>Cycloserine</td>
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<tr>
<td>Capreomycin</td>
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<tr>
<td>Ethambutol (EMB) in high doses</td>
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<tr>
<td>Quinolones</td>
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<tr>
<td>Clofazamine ? (slowly)</td>
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<td>Linezolid</td>
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### First Line Drugs

- Isoniazid
- Rifampin
- Rifabutin
- Rifapentine
- Ethambutol
- Pyrazinamide
Isoniazid (INH)

- **MOA:** bactericidal, it inhibits DNA synthesis of mycolic acids, which are important components of mycobacterial cell wall
- It is the most active drug for the treatment of tuberculosis
- A **prodrug,** which means it requires activation by enzyme (mycobacterial catalase-peroxidase KatG).
- After orally administered:
  - well absorbed
  - widely distributed in body
  - good CNS and macrophages penetration

INH

- Absorption decreased by food
- Metabolized by liver
- Excreted via urine
- $t\frac{1}{2} = 0.7$ to 4 hours (fast acetylators = 1 hr, slow acetylators = 3 hrs)
  - Polymorphism – genetically some populations will metabolize or breakdown INH more rapidly than others (slow, intermediate or rapid acetylators)
**INH Polymorphism**

- **Rapid acetylators (dominant trait)** – prone to hepatitis
  - U.S. Caucasian 24 – 50%
  - African-Americans 35%
  - Hispanics 40%
  - Japanese 67 – 80%
  - American Indian ~ 70%
- **Slow acetylators (recessive trait)** – prone to peripheral neuropathy
  - Egyptian: 80-90%
  - European, North American: 40-70%
  - Asian: 10-30%
  - Canadian Eskimo: 5%
- No significant clinical difference in treatment/dose, however, some studies suggested possibility of relationship with the incidence of adverse reactions

**INH**

- Follow LFTs in patients receiving INH: baseline, 1, 3, and 6 months. Discontinue if transaminase increase to greater than 3-5 times normal.
- Asymptomatic increase in ALT concentrations - 20% of patients on standard 4 drug regimen-treatment does not need to be modified but las monitored more frequently.
- Renal Dose: no adjustment needed
- Pregnancy category C
  - Consider safe in pregnancy, but the risk of hepatitis may be increased in the peripartum period
**INH**

- **ADR**
  - Peripheral neuropathy (10-20%)
    - Tingling and numbness
    - Concurrent pyridoxine administration with INH prevents most of these complications
    - Predisposing conditions: diabetes, uremia, malnutrition, HIV infection
  - Other side effects
    - Hemolytic anemia
    - Seizures
    - Psychosis
    - Lupus-like syndrome

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**Isoniazid - ADR**

- Hepatic
  - ↑ transaminase (AST & ALT) = 10-20% of the patients
  - Hepatitis = 2.1% over all incidence
  - 2.7% with RIF
  - < 20 yo – very rare
  - 3 x higher in those over 35
  - 4 x higher if daily alcohol
  - in one study 4.2% of cases were fatal
**INH**

- **Drug Interactions**
  - MAOI inhibitor (weak)
  - Histamines
  - P-450 inhibitor (CYP2C19, CYP3A4)
    - May increase the risk of toxicity of certain drugs such as anticonvulsants (e.g., phenytoin, carbamazepine) and some benzodiazepines (e.g., diazepam, triazolam)
  - B 6 (agonist)

- **Resistance**
  - Rapid resistance if used alone (10%) so combination therapy is required for active TB
  - Resistance is due to mutations/deletion in KatG gene which is required for activation of INH = providing protection of the bacterial cells
Rifampin

- Synthetic derivative of rifamycin and bactericidal
- MOA: binds to bacterial DNA-dependent RNA polymerase, and thereby inhibits RNA synthesis
- Oral administration, well absorbed, widely distributed in body; excellent tissue penetration
- CNS concentration is adequate only if meninges inflamed
- Metabolized by liver
- Excreted into bile and some in urine
- t\(\frac{1}{2}\) = 2-3 hours
- Renal: no dose adjustment
- Liver: no dose adjustment (but close monitoring)

Rifampin

- Broad-Spectrum
- Active against G+ cocci (including drug-resistant S. aureus)
- It can kill organisms that are poorly accessible to many other antibiotics, such as intracellular organisms and those sequestered in abscesses and lung cavities
- Uses: leprosy, other G+ infections, prophylaxis for meningitis caused by highly penicillin-resistant strains of pneumococci
- Resistance: due to target mutations in RNA polymerase (gene) leads to decreased binding, occurs readily
Rifampin

- **Adverse Drug Reactions:**
  - **GI** – anorexia, diarrhea, dysphagia (most common)
  - **Skin** – rash pruritis (6%)
  - **Arthralgias, myalgias** (fairly common)
  - Urine, sweat, tears and contact lenses may take on an **orange color** (harmless)
  - **Hepatic**
    - Hyperbilirubinemia (0.6%)
    - Hepatitis (0%- alone, 2.7% with INH)
  - Thrombocytopenia (< 0.1%)
  - Decreased thyroid, adrenal, vitamin D, etc

- **Adverse Reactions (cont.):**
  - Potent Inducer (CYP1A2, 2C9, 2C19, 3A4): will accelerate the metabolic clearance of many drugs including warfarin, corticosteroids, estrogens (including oral contraceptives), antiarrhythmics, theophylline, anticonvulsants, ketoconazole, cyclosporine, and others
  - Intermittent administration of rifampin (especially large doses) is associated with a flu-like syndrome, thrombocytopenia, hemolytic anemia, and renal failure
  - Has been rarely associated with drug-induced lupus
  - Pregnancy category C
Rifabutin (RBT, RBN)

- Second-line rifamycin derivative with longer half-life and fewer drug interactions than rifampin
- Trade Name: Mycobutin
- Use as a substitute for rifampin
- Reserve for patients who are receiving any medication having unacceptable interactions with rifampin or have experienced intolerance to rifampin
  - Same interactions as rifampin, but not as clinically significant
  - Can often be overcome by adjusting dosages
- Cross-hypersensitivity with rifampin
- Cross-resistance with rifampin (~95%)

Rifabutin

- Kinetics:
  - Widely distributed in body
  - Lung concentrations 5-10 times higher than serum levels
  - $t_{1/2} = 45$ hours
  - Has an active metabolite
  - Renal clearance <30%, reduce dose by 50%
Rifabutin

- Adverse Reactions:
  - Neutropenia (dose related)
  - GI
  - Hepatotoxicity: similar to Rifampin (<1%)
  - Skin: rash (<0.1%)
  - Orange discoloration of bodily fluids
  - Flu-like syndrome: rare (less than 0.1%)
  - Polyarthritis: arthralgia and/or myalgias (dose related)
  - Uveitis
    - 8% at higher doses, macrolides, protease inhibitors
  - Pregnancy category B

Rifapentine (RPT)

- Same MOA as rifampin (inhibition of RNA polymerase)
- Trade Name: Priftin
- Cross resistance to rifampin is likely
- $t_{1/2} = 13.2-14$ hours. The 25-O-desacetyl metabolite is active ($t_{1/2} = 13-24$ hours). Both the parent compound and the metabolite are highly protein bound (98%).
- Take with food (whereas rifampin and rifabutin should be taken on empty stomach)
- Use once weekly (for LTBI, combined with 900mg INH weekly given for 12 wks)
- Potent inducer like rifampin, so similar drug interactions
Rifapentine

- Adverse Reaction:
  - Rates of adverse reactions are similar to rifampin
  - An inducer of multiple hepatic enzymes – increases metabolism of coadministered drugs that are metabolized by these enzymes

- Safety in pregnancy or patients under 12 years old has not been established (teratogenic in lab animals)

Pyrazinamide (PZA)

- Bactericidal
- At neutral pH, it is inactive, but at pH 5.5, it inhibits tubercle bacilli and some other mycobacteria
- Quickly absorbed after oral administration
- Widely distributed in body tissues, including inflamed meninges
- It is used in combination with INH and RFP for short-term therapy to exert its activity against residual intracellular organisms that may cause relapse
- Pregnancy Category C – almost all/all of the first line drugs fall in this category
- Metabolized by liver
- Excreted in urine
- t½ = 8-12 hours (increased in hepatic/renal failure)
**Pyrazinamide (PZA) cont.**

- **Adverse Reaction:**
  - **Hepatotoxicity:** (~1%), liver function should be performed before and during therapy
  - **Nongouty polyarthralgia:** (up to 40%) rarely requires dosage adjustment or discontinuation of the drug
  - **Asymptomatic hyperuricemia:** but rarely causes acute gout, serum uric acid may therefore be used as marker for patient compliance
  - **Acute gouty arthritis:** very rare, stop the drug
  - **Skin:** rash, photosensitive dermatitis
- Renal Dosage: reduce dose in renal insufficiency

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**Ethambutol (EMB)**

- **Bacteriostatic (bactericidal at highest dose)**
- **MOA:**
  - Interferes with RNA, protein synthesis
  - Requires growing organism
- Well absorbed from the gut and widely distributed in all body tissues and fluids
- CNS concentration only if meninges are inflamed
- Excreted in urine (50%) and feces (20%)
- Renal dosing is needed to avoid ocular toxicity
- Pregnancy category C (safe in pregnancy according to CDC)
- Not used in children < 5 years old
Adverse Reactions:
- Optic neuritis: most common and serious (dose related, 18% if dose >50mg/kg/day)
  - blurred vision
  - central scotoma
  - red-green color blindness
  
  This toxicity occurs in less than 1% of the patients given 15mg/kg/day but increases with total daily dose, and it also seems worse with daily use as opposed to three times/week.
  
  Patient should be instructed to report any changes in vision

- Hyperuricemia: rare

- Peripheral neuritis: rare

Ethambutol

Combination Products

These products minimize inadvertent monotherapy and so may decrease the frequency of acquired drug resistance.

Less pills to take = less medication errors = decrease noncompliance

Good choice when DOT is not an option

<table>
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<tr>
<th>Rifamate</th>
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<tr>
<td>Isoniazid 150mg</td>
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<tr>
<td>Rifampin 300mg</td>
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<td>Pyrazinamide 300mg</td>
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</table>
Second-Line Drugs

- Second-line medications should only be used in patients unable to tolerate first-line medications, or in cases of organisms resistant to first-line medications
  - Streptomycin
  - Quinolones
  - Capreomycin
  - Cycloserine
  - PAS (para-aminosalicylic acid)
  - Ethionamide
  - Amikacin

Fluoroquinolones:

- Levofloxacin, Moxifloxacin and Gatifloxacin
- Use to treat drug-resistant TB or patients who cannot take first-line drugs due to side effects.
- Use in children is limited because of possible effects on bone and cartilage growth.
- SE: gastrointestinal, headache, rash, tendonopathy (rare) - tends to occur in patients >50, patients with renal disease undergoing hemodialysis, and patients receiving corticosteroids.
- CNS concentrations: 30-50% of serum concentrations
**Streptomycin (SM):**

- First antimicrobial drug used to treat TB
- Aminoglycoside antibiotic effective against most tubercular bacilli, but its activity is weaker than that of INH and RFP
- MOA: inhibition of protein synthesis (bactericidal)
- Penetrates into cells poorly, and drug-resistance is common
- At present, streptomycin is used when an injectable drug is desired, principally in individuals with severe, possibly life-threatening forms of tuberculosis, and in treatment of infections resistant to other drugs
- It is always given together with other drugs to prevent emergence of resistance

**Streptomycin (cont.)**

- Adverse Effects:
  - **Ototoxicity**: (vestibular, hearing disturbances), risk increases with age
  - **Neurotoxicity**
  - **Nephrotoxicity**: not as common as with amikacin or capreomycin
- Contraindicated in pregnancy (risk of fetal hearing loss)
- Poor CNS penetration
- Requires renal dosing and close monitoring
Polypeptide (not aminoglycoside) antibiotic

MOA: bactericidal, bind to the mycobacterial ribosome and inhibit protein synthesis (translation)

Cross-resistance with streptomycin is possible but not common

Contraindicated in pregnancy (risk of fetal nephrotoxicity and hearing loss)

Does not penetrate the CNS well

Renal dosing is required

Adverse Reactions:

- Nephrotoxicity – 20% to 25%
- Ototoxicity (especially in elderly or in patients with renal impairment)
- Others:
  - Rash
  - Leukopenia
  - Eosinophilia
  - Neuromuscular blockade
Cycloserine (CS)

- Bacteriostatic
- MOA: inhibition of cell-wall synthesis
- May be used on a temporary basis for patients with acute hepatitis in combination with other nonhepatotoxic drugs
- Administer on an empty stomach because food modestly decreases absorption
- Safety in pregnancy unestablished
- CNS concentrations are similar to serum regardless of inflammation
- Renal dosing is required

Cycloserine (cont.)

- Adverse Reactions:
  - CNS: headache, restlessness, psychosis, seizures, anxiety, confusion, memory loss, disorientation, depression
    - Seizures are especially common at doses >500mg/day. Pyridoxine 100-200mg/day may prevent neurotoxicity
    - Peripheral neuropathy
      add pyridoxine may prevent this
  - Contraindicated in in patients with major depressive disorder, anxiety, psychosis, pre-existing seizures, alcoholism or renal failure
Thioamide derivative, structurally similar to INH
- Ethionamide is a prodrug with the same target as INH, but is activated by a KatG-independent mechanism
- MOA: blocks the synthesis of mycolic acids
- Not cross-resistant with INH because the activation mechanism are different (most INH resistance is due to point mutations in the gene encoding KatG)
- Contraindicated in pregnancy
- CNS concentrations are similar to serum regardless of inflammation

**Ethionamide (ETA)**

- Adverse Reactions:
  - **Profound GI disturbances** (metallic taste, nausea, vomiting, anorexia, abdominal pain)
  - **Hepatotoxicity** (2% of patients)
  - **Neurotoxicity** (peripheral neuritis, optic neuritis, anxiety, depression, psychosis)
  - **Endocrine disturbances** (gynecomastia, alopecia, hypothyroidism, impotence)
Para-Aminosalicylic Acid (PAS):

- MOA: bacteriostatic, it interfere with mycobacterial folate biosynthesis
- Granule packets (sprinkle on acidic food like yogurt or apple sauce)
- PAS has been used safely in pregnancy, however no studies available in humans
- CNS concentration are 10-50% those achieved in serum, thus borderline useful for tuberculous meningitis
- Contraindicated in severe renal insufficiency
- Limited availability in US. No longer available through the CDC Drug Service

Para-aminosalicylic acid (cont.)

- Adverse Reactions:
  - Gastrointestinal most common (11%)
  - Hypersensitivity reactions
  - Hypothyroidism
  - Hepatotoxicity (rare) (0.3-0.5%)
  - Coagulopathy: a doubling of prothrombin time that seemed to be lessened by coadministration of streptomycin

Used infrequently because of poor tolerance and primary resistance
Drug Resistant TB

- MDR-TB (multi-drug resistant) is defined as resistance to INH and RIF, with or without resistance to other anti-TB drugs
- XDR-TB (extensively-drug resistant) is defined as resistance to at least INH and RIF (i.e., MDR-TB) plus resistance to any of the fluoroquinolones and any one of the second-line injectable drugs (amikacin, kanamycin and capreomycin)
- Drug resistance:
  - Primary resistance develops in persons initially infected with resistant organisms
  - Secondary resistance (acquired resistance) develops during TB therapy

Treatment of Resistant TB

- Treatment depends on drug sensitivity test results.
- **INH resistance:** treat with rifampin + PZA + ethambutol daily for 6 months. Add levofloxacin (500-1000mg qd) to strengthen the regimen for patients with extensive disease.
- **Rifampin resistance:** treat with INH + PZA + ethambutol daily for 9-12 months. Add levofloxacin (500-1000mg qd) to strengthen the regimen for patients with extensive disease. An injectable agent may be added in the initial 2 months of therapy for more extensive disease and/or to shorten the duration of therapy.
- **INH-Rifampin resistance:** treat with fluoroquinolone, PZA, ethambutol, injectable agent (aminoglycoside or capreomycin) ± fifth agent. Duration of therapy 18-24 months. Resectional surgery may be appropriate.
- **XDR-TB (extensively drug-resistant TB):** defined as strain of M. tuberculosis resistant to INH, rifampin, any fluoroquinolone, and an injectable agent. Associated with poor outcomes. Optimum treatment approach not yet established.
Treatment Problems

- Can’t Swallow Pills
- GI Intolerance
- Adverse Drug Reactions
- Drug Interactions
- HIV Disease
- Renal Failure
- Hepatitis
- Failure to Respond

Can’t Swallow:
- Use oral liquids
  - INH syrup, RIF, PZA, EMB (mixed with syrup/juice)
- Use injectables
  - INH, RIF, Aminoglycosides, Quinolone

GI Intolerance:
- Divide doses*, bedtime dosing, take with meals (*not typically recommended for a number of drugs)
- Initiate therapy with
  - H2 blockers, proton-pump inhibitors
- Pre-mEDIATE
  - Metoclopramide 5-10mg po 30 min before meds
  - Hydroxyzine 25-50mg po 30 min before meds
  - Lorazepam 0.5-1mg po 30 min before meds
ADR
- Gout/joint/muscle pain
  Allopurinol, probenecid
  NSAIDs
- Itching
  Hydroxyzine
  Diphenhydramine
- Insomnia
  Hydroxyzine
  Diphenhydramine
  Trazodone
  Bedtime dosing

Allergies
- Desensitization
  Low doses given
  frequently and gradually
  increasing in doses
  Use only where
  emergency treatment is
  available
  If future treatment is
  interrupted, may need
  to repeat the
  desensitization process

Management of ADR:

Seizures
- Suspend suspected
  agent pending resolution
  of seizures
- Initiate anticonvulsant
  therapy
- Increase pyridoxine to
  maximum daily dose
  (200mg/day)
- Restart at lower dose
- Discontinue and switch
to different agent

Peripheral Neuropathy
- Increase pyridoxine to
  200mg/day
- Change injectable to
  capreomycin
- Initiate therapy with
  tricyclic antidepressant
- Lower the dose
- Discontinue and switch to
different agent
Management of ADR:

- **Hepatitis**
  - Suspend all therapy pending resolution of hepatitis
  - Eliminate other potential causes of hepatitis
  - Consider suspending most likely agent permanently
  - Reintroduce remaining drugs one at a time with the most hepatotoxic agents first while monitoring liver function

- **Renal Toxicity**
  - Suspend suspected agent
  - Consider using capreomycin if an aminoglycoside had been the prior injectable in regimen
  - Consider dosing 2-3 times a week if regimen is available
  - Renal dosing based on creatinine clearance

- **Optic Neuritis:**
  - Stop Ethambutol
  - Refer patient to ophthalmologist
  - Usually reverses with cessation of ethambutol

- **Electrolytes Disturbances**
  - (Hypomagnesium, Hypokalemia):
    - Check potassium
    - If potassium is low, also check magnesium and calcium if hypocalcaemia is suspected
    - Replace electrolytes as needed
Nursing Implications:
❖ Obtain thorough medical history/assessment
❖ Baseline labs (liver functions, thyroid functions)
❖ Assess for contraindications (pregnancy, drugs interactions, liver/renal functions)
❖ Patient education
  • Compliance
  • Durations of therapy up to 24 months
  • Avoid alcohol
  • Personal health (nutrition, blood sugar...etc)
❖ Monitor SE

NEW DRUGS???
Why do we need new drugs to treat TB?

- Shorter overall treatment duration
- Lower relapse rates
- Development of regimens with fewer adverse effects, particularly less hepatotoxicity
- Development of regimens that can be given easily and safely in combination with antiretroviral therapy
- Development of regimens that are effective in treating MDR-TB/XDR-TB

TB drugs in clinical development

<table>
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<tr>
<th>Sponsor</th>
<th>Drug</th>
<th>Stage</th>
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<tr>
<td>Otsuka, Unitaid, NIAID</td>
<td>Delamanid</td>
<td>Phase 3</td>
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<td>TB Alliance</td>
<td>Pretomanid</td>
<td>Phase 3</td>
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<tr>
<td>Sequella, NIAID</td>
<td>Sutezolid</td>
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<tr>
<td>LegoChem Biosciences</td>
<td>LCB01-0371</td>
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New Drugs for TB: Conclusion

- More drugs in clinical development than at any time in the last 40 years
- Bedaquiline has been recently approved – the first new TB drug since rifampin
- Delaminid used for MDR treatment currently approved in Europe
- Multiple challenges in TB drug development
  - Combining novel agents
  - Clinical trials capacity
  - Length of trials
  - Funding

Thank You
1. Recommendations for Use of an Isoniazid-Rifampentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis infection. MMWR 2011
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